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10/535,746	05/20/2005	Judah Folkman	701039-055264	9640

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EXAMINER	
SCHUBERG, LAURA J	

ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
02/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/535,746	FOLKMAN ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-18,30,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-18,30,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/23/08 6/10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 8-18, 30, and 35-36 are presented for consideration on the merits.

Claims 1, 8, 15-18, 30 and 35-36 have been amended and claims 5 and 19 have been canceled.

Response to Arguments

Applicant's arguments filed 09/24/2008 have been fully considered but they are not persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicant argues that data supporting the claim limitations wherein an increase in the level of PF-4 from a first time point to a second time point is indicative of angiogenic disease in an individual is provided at figures 22c and 17 and 29.

This is not found persuasive because these figures do not provide for support for the early detection of any and all tumor-associated diseases or disorders as claimed by Applicant. The data is limited to specific *in vitro* cell types and does not fully support the broad scope of the claimed invention.

Applicant argues that the specification teaches that PF-4 is increased in platelets of individuals bearing tumors and teaches that by monitoring the levels of PF-4 in the platelets of women at risk for breast cancer, tumors may be detected earlier, perhaps before other symptoms or markers are detected.

This is not found persuasive because the passage cited by Applicant (paragraph 270) does not provide evidence that all tumor-associated diseases or disorders can be detected early by the claimed invention. The statements are prophetic and do not include any evidence that would enable one of skill in the art to practice the full scope of the claimed invention without undue experimentation.

Applicant argues that providing the levels of PF-4 at 6 months, 10 months and 1 year is not required for enablement. Applicant asserts that there is no further experimentation required in measuring the level of PF-4 at these time periods.

This is not found persuasive because these values are needed to provide guidance to one of skill in the art as to what levels indicate early detection of any tumor-associated disease or disorder.

Applicant argues that data supporting the claim limitations wherein an increase in the level of PF-4 combined with other angiogenesis regulators from a first time point to a second time point is indicative of tumor implantation in an individual is provided at figures 16-18 , 22A, 22C, and 29A-29H.

This is not found persuasive because Applicant has not established a clear cause and effect relationship between PF4 levels and tumors, just a correlation. That is, Applicant has shown that when there is a tumor, PF4 may be elevated in some instances, but Applicant has not shown that elevated PF4 means that there must be a tumor present.

Applicant argues that there is nothing in the '084 patent that suggests that the PF-4 in platelets from an individual may be monitored as a means for early indication of

a tumor in that individual. Applicant asserts that the '084 patent teaches away from the results presented in the instant application.

This is not found persuasive because the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). The '084 patent teaches the value of measuring PF-4 from isolated platelets and practices the method steps of isolating the platelets and measuring the PF-4 levels from the platelets. Repeating the measurements would be an obvious step albeit for a different reason than Applicant's. Applicant's claim limitations "wherein an increase in the level of PF-4 in the platelets from said second time point is indicative of the presence of a tumor in said individual" is not an active method step and thus is deemed an inherent property or effect of practicing the active method steps.

Priority

The current application filed on May 20, 2005 is a 371 of PCT/US05/14210 filed April 26, 2005. The information provided by the applicants appears to be consistent with the PTO data base.

Information Disclosure Statement

The IDS filed 4/23/2008 and 6/10/2008 have been received and are signed and considered, a copy of the PTO 1449 is attached to the following document. References lined through have been previously considered.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 8-18, 22, 30, and 35-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-15, and 24-29 of copending Application No. 11/304384. Although the conflicting

claims are not identical, they are not patentably distinct from each other because the claims of the instant application are drawn to isolating platelets at two different time points, analyzing levels of angiogenic regulator PF4 at each time point, and then comparing the levels at the two different time points. The claims of the instant application are further drawn to determining at least a second angiogenic regulator in the platelets. The claims of the '384 application are drawn to isolating platelets at two different time points, analyzing levels of at least two different angiogenic regulators (of which PF4 is one choice) at each time point, and then comparing the levels at the different time points. The claims of both applications are drawn to determining the angiogenic regulator levels in individuals having a genetic predisposition to cancer, having particular tumor suppressor genes, and those with particular types of cancer or other angiogenic diseases.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8-18, 30, 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting and

monitoring PF-4 levels in platelets, does not reasonably provide enablement for detecting a tumor-associated disease or disorder by detecting and analyzing PF-4 levels in platelets. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Practicing such a method would require the skilled artisan to invest undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' "(Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the relative skill of those in the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

N.B. MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

1-2 .Breadth of the claims and the nature of the invention..

In regards to the method of the invention and the breadth of the claims the broadest interpretation that applies is a method that detects a tumor-associated disease or disorder by comparing PF-4 levels from isolated platelets at two different time points in individuals. The claims are broad in that they encompass any disease or disorder associated with a tumor.

3-4. The state of prior art and the level of predictability in the art.

The prior art indicates that PF-4 inhibits angiogenesis and that regions of active angiogenesis *in vivo* preferentially bind rhPF-4 (see, for example, Hansell et al 1995). Furthermore, Borgstrom teaches that fluorescently labeled PF-4 intensely and specifically labeled capillaries growing into implanted breast tumors, and that human breast cancer cell lines possess considerable angiogenic activity (see, Borgstrom

2003). Borgstrom further teaches that there is currently no reliable information on *in vivo* angiogenic behavior of breast cancer, and that the results of the PF-4 labeling study in breast cancer were a prerequisite for the evaluation of PF-4 as an angiogenic marker.

5. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

6-7. The amount of guidance present and the existence of working examples.

Applicant does not provide any working examples in the instant specification regarding analyzing platelets for levels of PF-4 and comparing the levels of PF-4 from a first time point to a second time point wherein a change in the level of PF-4 in the platelets from the second time point indicates an angiogenic disease or disorder. Applicant provides no guidance as to what "a change" in the level of PF-4 means, and furthermore, Applicant does not relate PF-4 directly to cancer in general, breast cancer or to the tumor suppressor gene BRCA1. In addition, Applicant has not provided examples wherein the second time point is at least 6 months, 10 months or one year after the first time point with regard to PF-4 to demonstrate the early detection of a tumor-associated disease or disorder. Furthermore, Applicant does not provide any working examples or guidance for a method of analyzing platelets for PF-4 and at least one additional angiogenic regulator, wherein a change in the

level of PF-4 or the additional angiogenic regulator indicates an early tumor-associated disease or disorder. Applicant has not established a clear cause and effect relationship between PF4 levels and tumors, just a correlation. That is, Applicant has shown that when there is a tumor, PF4 may be elevated in some instances, but Applicant has not shown that elevated PF4 means that there must be a tumor present.

8. The quantity of experimentation necessary.

The amount of experimentation that is required is undue: while isolating platelets and analyzing the level of PF-4 is routine, a method of further comparing the levels of PF-4 at first and second time points to determine a change in levels for detecting the presence of a tumor and a tumor-associated disease or disorder is not routine and requires more experimentation. Applicant's disclosure lacks specific information on a range of tumors both benign and malignant as well as establishment of threshold levels or extent of increase in PF4 that indicates a tumor is present.

Therefore, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,8-18, 30, 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "early" in claim 1 is a relative term which renders the claim indefinite. The term "early" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For examination purposes "early detection" will be interpreted as detecting a tumor-associated disease or disorder prior to metastasis of the tumor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Komurasaki et al (US 5,847,084).

A method is claimed for the early detection of a tumor-associated disease or disorder in an individual comprising the steps of isolating platelets at a first time point, analyzing said platelets for the level of PF-4, isolating platelets at a second time point, analyzing said platelets for the level of PF-4, and comparing the levels of PF-4 from the first time point to the levels of PF-4 from said second time point, wherein an increase in the level of PF-4 in the platelets is indicative of the presence of a tumor.

Komurasaki et al beneficially teach a method of isolating platelets from blood samples and then eluting PF-4 from the platelets. Furthermore, Komurasaki et al beneficially teach that Western blotting can be used to quantify the PF-4 obtained from the platelets. In addition, Komurasaki et al teach that PF-4 has angiogenesis inhibitory activity in malignant tumors and that it has been effective for suppressing malignant tumor cells (see, for example, col. 1, lines 45-67, col. 3, lines 20-65 and col. 4, lines 20-45).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of isolating platelets and PF-4 as disclosed by Komurasaki et al, based upon the art-recognized method of monitoring patients' health conditions by comparing values of particular health parameters taken at one time point to those taken at a second time point. The result-effective adjustment of

particular conventional working conditions (e.g., using a particular means to isolate platelets and a means to analyze the level of PF-4 in the platelets) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole, was *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, as evidenced by the cited references, especially in the absence of evidence to the contrary.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg